Tuberous Sclerosis Alliance

RENAL MANIFESTATIONS IN TSC

The majority of individuals (greater than 80 percent) with tuberous sclerosis complex (TSC) will develop some form of renal (kidney) disease during their lifetime. There are three particular renal disorders in TSC: **renal cysts, renal angiomyolipoma** and **renal cell carcinoma**.

Renal angiomyolipomata, or angiomyolipomas, are usually the greatest concern in TSC. The blood vessels within angiomyolipomas are abnormal and can develop weak spots in their wall, called aneurysms, that can burst and lead to bleeding. About 20% of the time this bleeding is life-threatening. Renal angiomyolipomata occur in approximately more than 80 percent of TSC patients. Most of the time both kidneys are involved.

Renal cysts are often small, benign fluid filled "holes" in the kidney that occur in about 50 percent of individuals with TSC. These cysts, even if they are not very common, can lead to increased blood pressure, but usually they do not cause discomfort. However, sometimes the kidney is filled with cysts, and this can lead to kidney impairment and even kidney failure, requiring dialysis or transplantation.

Lastly, renal cell carcinoma, the least common renal association with TSC, is a cancerous growth of the kidney. Although it is very rare, such a lesion must be kept in mind.

Diagnosis

The current methods to diagnosis these renal abnormalities include renal ultrasonography, CT scanning and magnetic resonance imaging (MRI). These are all non-invasive procedures that are available in almost every major medical center. The renal ultrasound provides the least detailed image of the kidney, while the MRI provides the most detailed. In general, the ultrasound is sufficient to detect both renal cysts and fat-containing angiomyolipomas, but may not provide enough detail to accurately measure and follow the renal lesions and can miss lesions that lack the fat component.

The kidneys should be scanned, preferably with MRI, at the time of diagnosis, and at 2-3 year intervals if no cysts or angiomyolipomas are identified. If kidney lesions are identified, then the growth of these lesions should be followed using repeated MRI every year or two, unless symptoms develop or the lesion has an unusual growth pattern. For individuals with TSC who cannot have MRI scans, for example because they have a VNS or would need general aneasthesia, infrequent CT scans can be done to calibrate and correlate with ultrasound imaging. Repeat CT scans should be limited to reduce exposure to iodinated radiocontrast and radiation. Imaging is critical however to assess if kidney lesions are present and/or if there has been a change in any of the existing kidney lesions.

Renal Cysts

Often renal cysts do not become apparent on CT scans or ultrasound until adulthood. Usually the cysts do not cause symptoms, but can lead to hypertension (high blood pressure). When the cysts are very numerous, renal-related signs and symptoms can arise including hematuria (bloody urine) and nephrolithiasis (kidney stones). Often the best drugs to use to lower the blood pressure in this situation are either angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Controlling blood pressure is very important, because having an elevated blood pressure can accelerate the loss of kidney function when the kidneys are filled with cysts. If kidney failure occurs, renal replacement therapy such as dialysis or transplantation is necessary.

How kidney cysts develop is not known. The TSC genes are tumor suppressor genes. Normally, tumor suppressor genes prevent excess cell growth. When the tumor suppressor genes are inactivated by mutations, cell growth is unchecked, leading to tumors. Cysts may, therefore, be the result of excess growth of kidney epithelial cells, which surround a fluid-filled cavity.

Some children and adults with TSC and severe cystic kidneys can have mutations (changes in the DNA) of both the TSC2 gene on chromosome 16 and the gene for polycystic kidney disease (PKD1), which lies right next to the TSC2 gene. Mutations in the PKD1 gene cause a disease called autosomal dominant polycystic kidney disease (ADPKD). Individuals with ADPKD, which is six times more common than TSC, most often develop kidney failure in adulthood. Individuals with mutations of both the TSC2 and PKD1 genes, severe kidney disease can develop in infancy or early childhood and renal failure most often occurs in early adulthood.

Renal Angiomyolipomas

Angiomyolipomas are named because they consist of blood vessels (“angio”), smooth muscle (“myo”) and fat (“lipoma”). Usually angiomyolipomas are multiple and occur in both kidneys. The presence of fat in angiomyolipomas often allows them to be distinguished from other renal tumors by MRI, CT or ultrasound imaging. Not uncommonly, angiomyolipomas do not contain fat, which can sometimes cause confusion in the diagnosis.

Studies suggest that angiomyolipoma size may be associated with symptoms. In one study, most, but not all individuals with tumors less than 4 cm in diameter had no symptoms, while approximately 90 percent of individuals with a tumor greater than or equal to 4 cm appeared to have symptoms. These symptoms most commonly included abdominal or back pain, nausea and vomiting and fever. For the individual who is non-verbal, this may be present as irritability and vomiting. However, bleeding or rupture rarely occurred in children; larger tumors occurred at an older age (greater than 10 years of age). It appeared in the limited number of individuals followed in several studies that angiomyoliopama in TSC patients continued to grow. The risk of hemorrhage appears to be caused by the abnormal blood vessels that can form defects called aneurysms.

Our understanding of the growth of renal angiomyolipoma and TSC is in its infancy and we will have further information in a few more years. The real danger of a large angiomyolipoma is that it can have aneurysms that can rupture and bleed. This bleeding can be significant and occasionally life threatening. Therefore, diagnosis and treatment guidelines have been

proposed to initially identify which individuals have kidney involvement in TSC and then, depending on the extent (or size) of this involvement, propose either close surveillance or some form of intervention.

It is recommended that individuals with TSC have an initial diagnostic radiologic imaging evaluation with an MRI if possible, or a CT to identify patients with kidney involvement. Then, depending on the size of the involvement, further management can be recommended. Individuals with TSC and angiomyolipomas less than 4 cm would benefit from repeat renal imaging every one to two years. If the angiomyolipoma appears to grow or become a source of symptoms, then some intervention should be strongly considered. This may include an embolization of the blood vessel that is "feeding" the angiomyolipoma. Sometimes surgery is required but this should be avoided if at all possible, because most individuals with TSC will develop multiple angiomyolipomas of both kidneys and repeated surgical removal can lead to loss of kidney function. As of April 26, 2012, adults with TSC and renal angiomyolipoma not requiring immediate surgery may be candidates for treatment with Afinitor® (everolimus) tablets to shrink and prevent further growth of angiomyolipomas. In individuals with TSC and an angiomyolipoma greater than 3 cm, because of the high risk of further growth and the development of symptoms, consideration should be given to oral therapy with everolimus.

For those who do not want to have any form of intervention, they should be aware of the type of symptoms that are associated with bleeding from the angiomyolipoma. This includes new significant back or abdominal pain, nausea, vomiting and fever. If these growths involve both kidneys, renal failure is a possibility. If kidney function became so poor as to not sustain life, then dialysis or transplantation would be indicated.

Renal Cell Carcinoma (Kidney Cancer)

Over the past 20 years, there have been at least 25 published reports of kidney cancer occurring in individuals with TSC. Drs. Bjornsson, Short, Kwiatkowski and Henske (1996) studied six individuals with kidney cancer and TSC. Their study confirmed previous reports that kidney cancer in individuals with TSC occurs on average at an earlier age than in individuals who do not have TSC. This suggests that individuals with TSC may have a higher risk of kidney cancer than the general population. Some TSC-associated cancers have different microscopic features from the most common form of kidney cancer in individuals who do not have TSC.

The risk of kidney cancer in TSC is much lower than the risk of angiomyolipomas. Sometimes it is very difficult or impossible to distinguish between an angiomyolipoma and a carcinoma using a CT scan. A biopsy may be very important in these situations. As always, surgery to the kidney should be avoided unless absolutely necessary. Additional studies are needed to determine the exact risk of kidney cancer in individuals with TSC and how best to screen for kidney cancer.

Summary

In summary, there are multiple different ways that the kidney can be affected in TSC. Angiomyolipoma is clearly the most common and likely to cause symptoms. With careful evaluation, monitoring and appropriate intervention, which should be performed by a team with TSC experience, many individuals with TSC can maintain normal kidney function.

Additional Online Resources

National Kidney Foundation: www.kidney.org

Kidney and Urology Foundation: www.kidneyurology.org

Polycystic Kidney Disease Foundation: www.pkdcure.org

Reviewed and updated by Elizabeth Petri Henske, M.D., Brigham and Women's Hospital, Harvard Medical School and Dana Farber Cancer Institute, Boston, MA, John J. Bissler, M.D., LeBonheur Children's Hospital and St. Jude Children's Research Hospital, Memphis, TN, and David H. Ewalt, M.D., Dallas, TX. November 2013.

***This publication from the Tuberous Sclerosis is intended to provide basic information about tuberous sclerosis complex (TSC). It is not intended to, nor does it, constitute medical or other advice. Readers are warned not to take any action with regard to medical treatment without first consulting a health care provider. The TS Alliance does not promote or recommend any treatment, therapy, institution or health care plan.*